

# Analysis of Steady-State Protein Homeostatic Regulatory Mechanisms in Perturbed Environments

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## ABSTRACT

Nine different protein homeostatic regulatory mechanisms were analyzed for their ability to maintain a generic protein P within a specified range of a set-point steady-state concentration while perturbed by external processes that altered the rates at which P was produced and/or consumed. Steady-state regulatory effectiveness was defined by the area within a rectangular region of “perturbation space”, where axes correspond to rates of positive and negative perturbations. The size of this region differed in accordance with the regulatory elements composing the homeostatic mechanism. Such elements included basic negative feedback control of transcription (in which P, at some high concentration relative to its set-point value, binds to the gene G encoding it, thereby inhibiting transcription), cooperative negative feedback (two P’s bind sequentially to G), and dimerization feedback (a P<sub>2</sub> dimer binds to G). Two homeostatic mechanisms included a cascade structure, one with and one

without translational feedback control. Another mechanism included feedback control of P degradation. Finally two mechanisms illustrated the limits of regulatory systems. One lacked any regulatory elements (and included only an invariant rate of P synthesis and degradation) while the other assumed perfect (Boolean) regulation, in which transcription is completely inhibited at  $[P] > [P]_{sp}$  and is fully operational at  $[P] < [P]_{sp}$ .

Although such systems are widely known, the analytical expressions developed herein allowed quantitative comparisons. These expressions were evaluated at values typical of the average protein in *Escherichia coli*. A method for building regulatory networks by linking semi-independent regulatory modules is discussed.